



US009636377B2

(12) **United States Patent**
Marion et al.

(10) **Patent No.:** **US 9,636,377 B2**
(45) **Date of Patent:** **May 2, 2017**

(54) **COMPOSITIONS AND METHODS FOR THE TREATMENT OF RETINAL DEGENERATION**

(71) Applicant: **UNIVERSITE DE STRASBOURG**,
Strasbourg (FR)

(72) Inventors: **Vincent Marion**, Schiltigheim (FR);
Anaïs Mockel, Strasbourg (FR); **Hélène Dollfus**, Strasbourg (FR)

(73) Assignee: **UNIVERSITE DE STRASBOURG**,
Strasbourg (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/380,493**

(22) PCT Filed: **Feb. 25, 2013**

(86) PCT No.: **PCT/EP2013/053724**

§ 371 (c)(1),

(2) Date: **Aug. 22, 2014**

(87) PCT Pub. No.: **WO2013/124484**

PCT Pub. Date: **Aug. 29, 2013**

(65) **Prior Publication Data**

US 2015/0038432 A1 Feb. 5, 2015

Related U.S. Application Data

(60) Provisional application No. 61/602,863, filed on Feb. 24, 2012.

(51) **Int. Cl.**

A61K 38/07 (2006.01)

A61K 31/19 (2006.01)

A61K 45/00 (2006.01)

A61K 31/155 (2006.01)

A61K 45/06 (2006.01)

A61K 38/22 (2006.01)

A61K 38/55 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 38/07** (2013.01); **A61K 31/155** (2013.01); **A61K 31/19** (2013.01); **A61K 38/2278** (2013.01); **A61K 38/55** (2013.01); **A61K 45/00** (2013.01); **A61K 45/06** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

PUBLICATIONS

Adams et al. ("The Retinal Cilopathies" Review Article; Ophthalmic Genetics, 28; 113-125, 2007).*

Boyce, M., et al., "A Selective Inhibitor of eIF2α Dephosphorylation Protects Cells from ER Stress," *Science*, Feb. 11, 2005, vol. 307, pp. 935-939.

Di Sano, F., et al., "Endoplasmic Reticulum Stress Induces Apoptosis by an Apoptosome-dependent but Caspase 12-independent Mechanism," *The Journal of Biological Chemistry*, Feb. 3, 2006, vol. 281, No. 5, pp. 2693-2700.

Mendes, C.S., et al., "ER stress protects from retinal degeneration," *The EMBO Journal*, 2009, vol. 28, No. 9, pp. 1296-1307.

Nakagawa, T., et al., "Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-β," *Nature*, Jan. 6, 2000, vol. 403, pp. 98-103.

Shiraishi, H., et al., "ER stress-induced apoptosis and caspase-12 activation occurs downstream of mitochondrial apoptosis involving Apaf-1," *Journal of Cell Science*, 2006, vol. 119, No. 19, pp. 3958-3966.

Tsaytler, P., et al., "Selective Inhibition of a Regulatory Subunit of Protein Phosphatase 1 Restores Proteostasis," *Science*, Apr. 1, 2011, vol. 332, pp. 91-94.

Walter, P., et al., "The Unfolded Protein Response: From Stress Pathway to Homeostatic Regulation," *Science*, Nov. 25, 2011, vol. 334, pp. 1081-1086.

Yoneda, T., et al., "Activation of Caspase-12, an Endoplasmic Reticulum (ER) Resident Caspase, through Tumor Necrosis Factor Receptor-associated Factor 2-dependent Mechanism in Response to the ER Stress," *The Journal of Biological Chemistry*, Apr. 27, 2001, vol. 276, No. 17, pp. 13935-13940.

Zaghloul, N.A., et al., "Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy," *Journal of Clinical Investigation*, Mar. 2009, vol. 119, No. 3, pp. 428-437.

Griciuc, A. et al. "ER stress in retinal degeneration: a target for rational therapy?" *Trends in Molecular Medicine*, Aug. 1, 2011, pp. 442-451, vol. 17, No. 8.

Yang, L.-P. et al. "Endoplasmic Reticulum Stress Is Activated in Light-Induced Retinal Degeneration" *Journal of Neuroscience Research*, Mar. 1, 2008, pp. 910-919, vol. 86, No. 4.

Shen, Y. et al. "Effect of Guanabenz on Rat AMD Models and Rabbit Choroidal Blood Flow" *The Open Ophthalmology Journal*, Jan. 1, 2011, pp. 27-31, vol. 5.

Bown, C. D. et al. "Regulation of ER stress proteins by valproate: therapeutic implications" *Bipolar Disorders*, Jun. 14, 2002, pp. 145-151, vol. 4.

Clemson, C. M. et al. "Therapeutic potential of valproic acid for retinitis pigmentosa" *British Journal of Ophthalmology*, Jan. 1, 2011, pp. 89-93, vol. 95, No. 1.

Mockel, A. et al. "Pharmacological Modulation of the Retinal Unfolded Protein Response in Bardet-Biedl Syndrome Reduces Apoptosis and Preserves Light Detection Ability" *Journal of Biological Chemistry*, Oct. 1, 2012, pp. 37483-37494, vol. 287, No. 44.

Written Opinion in International Application No. PCT/EP2013/053724, Apr. 15, 2013, pp. 1-9.

(Continued)

Primary Examiner — James H Alstrum Acevedo

Assistant Examiner — Tara Martinez

(74) Attorney, Agent, or Firm — Saliwanchik, Lloyd & Eisenschenk

(57) **ABSTRACT**

The present invention relates to a pharmaceutical composition comprising an inhibitor of eIF2α, a compound increasing the expression and/or activity of protein BiP and/or an inhibitor of Caspase-12, preferably an inhibitor of eIF2α and a compound increasing the expression and/or activity of protein BiP. The present invention also relates to pharmaceutical compositions and methods for treating retinal degeneration related to ciliary dysfunction.

5 Claims, 18 Drawing Sheets
(15 of 18 Drawing Sheet(s) Filed in Color)